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10/538,916	06/13/2005	Fumio Nomura	050337	8854

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,916	NOMURA ET AL.	
	Examiner	Art Unit	
	Agnes B. Rooke	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-19* is/are pending in the application.

4a) Of the above claim(s) *1 in part, 3, 7-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's election without traverse of Group I (claims 1-3, 5-6, and 17-18) filed on 10/11/2007 is acknowledged. Also, Applicants further elect a marker species of SEQ ID NO:1, and thus claims 1, 2, 5, 6, and 17 read on this election and are thus examined.

Status of Claims

2. Claim 4 is canceled. Claims 1-3 and 5-19 are pending. Claims 1, 2, 5, 6, and 17 are under examination. Claim 1 is examined in part (see objection below). Claims 3, 7-16, 18, and 19 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Priority

3. This application is a 371 of PCT/JP03/16600 filed on 12/24/2003, which claims foreign priority to JAPAN 2002-371959 filed on 12/24/2204.

The priority is given to the 371 application filed on 12/24/2004, but the priority is not given to the foreign JAPAN application because the certified copy of the foreign document is not presently on file.

Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority based on priority papers filed in parent Application JAPAN 2002-371959 under 35 U.S.C. 119(a)-(d) or (f), a claim for such foreign priority must be timely made in this application. To satisfy the requirement of 37 CFR

1.55(a)(2) for a certified copy of the foreign application, applicant may simply identify the application containing the certified copy.

Specification

4. The specification is objected to because of the following informalities:

The first paragraph in the specification should include the priority information to match the Bib Data Sheet.

Information Disclosure Statement

5. The Information Disclosure Statements filed on 13 June 2005, 27 July 2005, and 17 August 2006 have been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and a copy is attached to the instant Office action.

Drawings

6. Drawings filed on 13 June 2005 has been accepted by examiner.

Objection to Claims

7. Claim 1 is objected to because non-elected subject matter is not cancelled from the elected claim 1. Applicants elected SEQ ID NO:1 where the sequence according to the claims and the specification has a molecular weight of 5.9 kDa, and the non-elected SEQ ID NO:2 has a molecular weight of 7.8 kDa. As currently presented, claim 1 claims a protein that has 7.8 kDa thus is in reference to the non-elected subject matter, SEQ ID NO:2. Claim 1 is examined in part in relevance to elected SEQ ID NO:1.

Claims 2 and 17 are objected to because the proper way to express the homology is "a protein having at least 90% homology with said amino acid" for example. Therefore, proper correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1, 2, 5, 6, and 17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1, 2, 5, 6, and 17 are drawn to a protein or a marker protein, which reads on a product of nature. The claims should be amended to indicate the hand of the inventor, for example the insertion of "isolated" or "purified" in connection with the protein to identify a product not found in nature (see MPEP 2105).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 2, 5, 6, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 17 are indefinite because it is not clear how the molecular weight was determined, thus further clarification is needed for example, is the molecular weight determined via SDS PAGE or ELISA is necessary in the claims. Therefore, since the amino acid sequence is not provided in this claim, the molecular weight should be characterized as being measured by the parameters as mentioned above. Claims 2, 5, 6 are included in this rejection because they depend from the independent claim 1 and do not cure the deficiencies of the independent claim.

Claim 6 is indefinite because it is not certain how the marker will diagnose "alcoholic liver trouble or alcohol dependence" since those terms are not in reference to a particular disorder or a specific symptoms or targets for the marker that is being claimed. Therefore, further specification of specific targets for diagnosing the liver disease in reference to an alcohol should be further provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 2, 5, 6, and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is directed to a protein marker that has molecular weight of 5.9 kDA and its variants that have the function of being a protein marker and being used

in diagnosing of liver disease (claims 1 and 17) where the SEQ ID NO;1 and its variants are claimed (claim 2) where the protein marker is used in diagnosis of liver diseases connected with alcoholism (claims 5 and 6).

However, no specific function is presented in reference to the SEQ ID NO:1 or its variants or a protein that has 5.9 kDA. The variants are characterized as being protein markers however this function is not sufficient enough to satisfy the written description requirement. One skilled in the art knows that each protein or its fragment can be a marker to a disease. However, here, there is no correlation between the structure of the fragments or variants of SEQ ID NO:1 and their function, besides being generally a protein marker.

Additionally, the instant specification does not demonstrate possession of said different variants of a protein having molecular weight of 5.9 kDa, or variants of SEQ ID NO:1. Further, the variants of the 5.9 kDa protein or SEQ ID NO:1 do not necessary have the desired function, since as noted in claim 2, several deletions, additions, substitutions, can be made to the variants at issue, for example. The examples disclosed in the specification discuss only 5.9 kDA (elected invention) and 7.8 kDa or 28 kDa (non-elected inventions). But there are no examples of different variants tested or described specifically.

A representative number of species means that the species which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of

drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus of different variants of a protein having molecular weight of 5.9 kDa (SEQ ID NO:1) could include non-functional proteins or proteins with a different function than the one described in regards to SEQ ID NO:1 as being a marker for any liver disease, where the disease itself is not specifically defined in claims 1, 2, or 17, for example. Only claims 5 and 6 mention liver disease as being focused on diseases caused by drinking. Therefore, the genus of claimed polypeptides encompasses widely variant species, and thus there is no nexus between the structure of potential distinct variants and their function.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure

of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

11. Claims 1, 2, 5, 6, and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein having molecular weight of 5.9 kDa or SEQ ID NO:1 (as elected), does not reasonably provide enablement for any variants of these proteins where several additions or substitutions or deletions are provided in the sequence as disclosed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These

factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified number of variants of the protein having 5.9 kDa or SEQ ID NO:1, where several addition, substitutions or deletions can be made to the claimed sequences. However, the claimed different variants once modified may not have the same properties of the native/wild-type protein or retain the same function. Further, the claims or specification does not indicate where variations will occur or what variations can be tolerated in the sequence. The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified or if said protein will be functional or exhibit the same properties or characteristics as the native protein. In the instant application, the reference to potential variants in the claims is insufficient to determine a chemical structure for the variants encompassed in the claim and thus it is uncertain whether they would be functional. Additionally, there is no data provided demonstrative of a particular portion of the structure that must be conserved. Therefore, the claims encompass variants/fragments that may not have any biological activity. Due to the large quantity of experimentation necessary to generate the infinite number of variants/fragments recited in the claims

and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The

instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (J. Bacteriology, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. are small compared to those contemplated and encompassed by the claimed invention.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in

the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants/fragments The claims broadly read on any fragments or different longer or shorter variants formed by addition, substitution or deletion, an thus no support in the specification is provided. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable

correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Therefore, absent direction/guidance regarding whether the structure of the cannulae polypeptide can tolerate the modifications contemplated a non-functional protein may result and one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims. In addition, absent direction/guidance regarding the heterologous polypeptide or peptide one of skill in the art would not be able to make the several variants that would retain a function as being a marker to a specific liver disease connected with alcoholism.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a

manner that reasonably correlates with the scope of the claims, to be considered enabling.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 2, 5, 6, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Garner et al. (U.S. 5,639,940).

Garner et al. teach materials and methods for producing fibrinogen (See abstract).

In columns 25-30, Garner et al. disclose the amino acid sequence that has 644 amino acids, and where the sequence comprises the instant SEQ ID NO:1. (See columns 25-30 in reference to amino acids 576-629 specifically).

Claims 1, 2, and 17 are rejected because they claim a protein having molecular weight of 5.9 kDa that is a SEQ ID NO:1 (claim 1) and Garner et al. teach a sequence that comprises SEQ ID NO:1 (claims 2 and 17).

Claims 5 and 6 are included in this rejection because they include an intended use of the protein being claimed, however the claims do not refer to a method, but to a composition of SEQ ID NO:1 and its different variants.

13. Relevant prior art of record is not part of the instant rejection but is part of the examiner's notes regarding search results: U.S. 5639940, 6416963, 6900016 (100% match to the instant SEQ ID NO:1)

Conclusion

14. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

AR

HOPE ROBINSON
PRIMARY EXAMINER